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Tumour infiltration depth ⩾4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma

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SUMMARY

Patients with pT1cN0 oral squamous cell carcinomas (OSCC) are generally not treated with a neck dissection (ND). However, in 25% of cN0 patients, nodal metastases become apparent during follow-up. Infiltration depth of the primary tumour has been consistently associated with the presence of nodal metastasis, but proposed cut-off depths for performing a ND vary considerably. The aim of this study was to explore the infiltration depth as predictor for the nodal status and to recommend a cut-off depth for performing a ND.

From our database of 351 primary oral carcinomas, we selected all pT1–2 tumours ($n = 246$). Infiltration depth was measured in 212 cases. Neck status was determined by histopathological examination of the dissection specimen, or by at least two years of follow-up.

Mean infiltration depth was 5.49 mm (95% CI: 4.86–6.12) in the N0 and 8.40 mm (95% CI: 7.38–9.43) in the N+ group ($p < 0.001$). cN status, lymphovascular invasion and infiltration depth were the only independent predictors for nodal status in multiple logistic regression. ROC-analysis on pT1cN0 tumours resulted in an optimal cut-off for the prediction of the nodal status at a depth of 4.59 mm. This cut-off identified a subgroup of patients at increased risk for nodal metastasis (OR = 8.3) and with significantly shorter survival.

Tumour infiltration depth is an independent predictor for nodal status in pT1–2 OSCC. In pT1cN0 tumours, a cut-off at 4.59 mm results in the best predictive value.

We recommend an infiltration depth of ⩾4 mm as an indication to perform a neck dissection in pT1cN0 OSCC.

Introduction

Treatment of the clinically N0 (cN0) neck is a dilemma in oral squamous cell carcinoma (OSCC) patients, especially in those suffering from small (T1–2) tumours. When considering all stages of OSCC, occult nodal metastases are present in up to 50% of cases,[1,2] even after clinical and radiological assessment by experienced head–neck oncologists. Not every cN0 tumour harbours the same risk for metastases, therefore it is not ethical to consider every patient for an elective neck dissection, due to the associated morbidity.[3] Moreover, performing a neck dissection might remove a natural barrier for tumour spread, which is of particular importance in OSCC, where recurrences and second primaries are frequent.[4] Therefore, an elective neck dissection is generally considered in cN0 patients when the risk for occult metastasis, is considered greater than 20%.[5] This risk assessment focuses mainly on T status and localization of the primary tumour.[2] Despite these additional criteria, still 20–30% of the cN0 patients considered low risk, and who are consequently not treated with a neck dissection, develop metastases during follow-up.[6]

Research in head–neck oncology has focused on finding additional predictors for the presence of occult nodal metastases, such as lymphovascular invasion,[1] intratumoural vessel density,[7,8] the

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presence of various immunohistochemical or molecular markers[9] and tumour infiltration depth.[10]

Currently, only tumour infiltration depth is consistently associated with nodal metastases and has an independent predictive value, as reviewed recently.[10,11] However, the depth that is suggested as cut-off for deciding to treat the neck varies greatly (1.5–10 mm) in literature.[10] There are several explanations for this variation. First, different definitions of infiltration depth are used, either measuring the distance from the deepest level of invasion to the tumour surface (tumour thickness) or measuring from the deepest level of invasion to the reconstructed mucosal surface (tumour infiltration depth). In many studies it is not clear which definition was applied. Second, studies suffer from the use of small groups ($n \leqslant 50$)[12–14] or widely differing tumour localizations.[15] Finally, cut-off depths are frequently subjectively chosen[12,14,16,17] or analysis is done on categorical rather than on continuous measurement data.[18,19]

The aim of this study was to explore the value of infiltration depth for predicting metastases in pT1–2 OSCC and to determine the optimal cut-off depth for performing an elective neck dissection. From a large cohort of patients, we selected a homogeneous group of pT1–2 OSCC, measured infiltration depth and performed rigorous statistical analyses to find the most optimal cut-off for performing a neck dissection.

Materials and methods

Patient selection

From the database of the Netherlands Cancer Registry, all records with the following criteria were retrieved: oral primary tumour location (ICD-O-3[20] locations C02.0–6.9), histologically proven squamous cell carcinoma, diagnosed between 1997 and 2008, treated in the UMC Groningen by resection of the primary tumour without prior head–neck or systemic oncological treatment ($n = 351$: 246 pT1–2 and 105 pT3–4 tumours). Information was collected regarding patient characteristics (e.g. previous cancer treatments, co-morbidities, follow-up, recurrences, date and cause of death), clinical tumour characteristics (e.g. localization, synchronicity, cTNM, method of nodal diagnosis, treatment), and pathological tumour characteristics (e.g. pTNM, histology, perineural and lymphovascular invasion, margin status).

All tissue blocks and haematoxylin and eosin (HE)-slides were retrieved from the archives of our department. All histopathological diagnoses were revised.

For this study we selected all pT1 and pT2 first primary oral tumours of which clinicopathologic data regarding nodal status were available.

Determination of nodal status

Clinically the nodal status is assessed by palpation of the neck combined with imaging (CT or MRI). When indicated, PET or ultrasound (with aspiration cytology) may be performed.

For patients who had received a neck dissection, we considered the pathological N status to be the "true N status". For patients who had not received a neck dissection (watchful waiting group), at least two years of follow-up data were examined for the development of nodal metastases. Because imaging is not performed routinely during follow-up, nodal metastases were initially diagnosed clinically, and always proven by fine needle aspiration cytology. In our institution, watchful waiting (return visits every 6 weeks), is performed on pT1cN0 OSCC with low risk for nodal metastases.

Measurement of infiltration depth

Infiltration depth was measured by an experienced head–neck pathologist, using digital microscopic imaging and computerized measurements (RVC, Research Assistant 6, Soest, The Netherlands). Infiltration depth was defined as the maximum depth of tumour infiltration (millimetres) below the mucosal surface. In case of ulcerated or exophytic tumours, the reconstructed mucosal surface was used.[10,21] Infiltration depth was measured on representative slides with the deepest infiltration.

Statistical analysis

Statistical analysis was performed with PASW 18.0. Categorical data were compared using the Chi-square test. Univariate and multiple logistic regression was used to assess the relationship between multiple predictor variables and the N status. Receiver–Operator-Curve (ROC) analysis was performed to determine the infiltration depth cut-off for the optimal prediction (highest sum of sensitivity plus specificity) of nodal metastases. Survival was analyzed by Kaplan–Meier analysis and the log-rank test. Hazard Ratios were calculated by Cox regression. Tests were performed two-tailed. $p < 0.05$ was considered significant.

Results

Study population

In total, 246 patients met the inclusion criteria of this study (pT1–2 OSCC). Cases were excluded due to synchronous multiple tumours ($n = 3$), irretrievable HE-slides ($n = 12$) or unreliable assessment of infiltration depth ($n = 19$). Therefore, 212 patients were included in this study. 174 patients were treated with a neck dissection, resulting in 102 pN0 and 72 pN+ dissections. Thirty-eight patients did not undergo a neck dissection (watchful waiting group). Median follow-up for these patients was 56.5 months. Seven patients (18%) developed nodal metastases.

The distribution of sex, age at diagnosis and tumour site (except for floor of mouth tumours) was comparable between the neck treated and watchful waiting groups (Table 1). Watchful waiting was performed in 38 (36%) of 106 pT1cN0 tumours. Main reasons for not performing watchful waiting were: a cT status >1 (33 cases), and floor of mouth localization with clinical involvement of the duct of the submandibular gland (30 cases; data not shown).

Infiltration depth distribution

The mean infiltration depth of the true-N0 group was 5.49 mm (95%CI: 4.86–6.12) which was significantly different from the true-N+ group at 8.40 mm (95%CI: 7.38–9.43) ($p < 0.001$; Fig. 1). When considering only the tumours that had been treated by watchful waiting ($n = 38$), mean infiltration depth in the true-N0 group was 3.32 mm (95%CI: 2.60–4.04) and in the true-N+ group 5.76 mm (95%CI: 2.93–8.58) ($p = 0.059$).

Infiltration depth is an independent predictor for true N status

In the total group ($n = 212$), cN status, pT status, perineural invasion, lymphovascular invasion and infiltration depth were significant predictors for the true N status (Table 2). Multiple logistic regression revealed only cN status (OR = 13.4; 95%CI: 5.5–32.9), lymphovascular invasion (OR = 3.8; 95%CI: 1.1–13.2) and infiltration depth (OR = 1.12 per millimetre; 95%CI: 1.03–1.23) as independent predictors for the true N status. These three variables were also independent predictors in the neck treated group ($n = 174$). In the

Table 1
Population characteristics ($n = 212$).

	Total population	Neck treated patients	Watchful waiting patients
Total tumours	212 (100)	174 (100)	38 (100)
Total patients	212 (100)	174 (100)	38 (100)
Sex			
Male	119 (56)	95 (55)	24 (63)
Female	93 (44)	79 (45)	14 (37)
Age at diagnosis (years)			
Median	61.5	61.5	61.5
Range	25–94	25–94	32–77
Site			
Tongue	108 (51)	81 (47)	27 (71)
Gum	15 (7)	12 (7)	3 (8)
Floor of mouth	64 (30)	63 (36)	1 (3)
Cheek mucosa	7 (3)	5 (3)	2 (5)
Retromolar area	12 (6)	9 (5)	3 (8)
Other	6 (3)	4 (2)	2 (5)
cN stage			
0	162 (76)	124 (71)	38 (100)
+	50 (24)	50 (29)	
Neck dissection			
Yes	174 (82)	174 (100)	
No (watchful waiting)	38 (18)		38 (100)
pT status			
1	123 (58)	85 (49)	38 (100)
2	89 (42)	89 (51)	
True N status			
0	133 (63)	102 (59)	31 (82)
+	79 (37)	72 (41)	7 (18)
Infiltration depth (mm)			
Median	6.00	6.50	3.15
Range	0.1–20.0	0.1–20.0	0.80–9.00

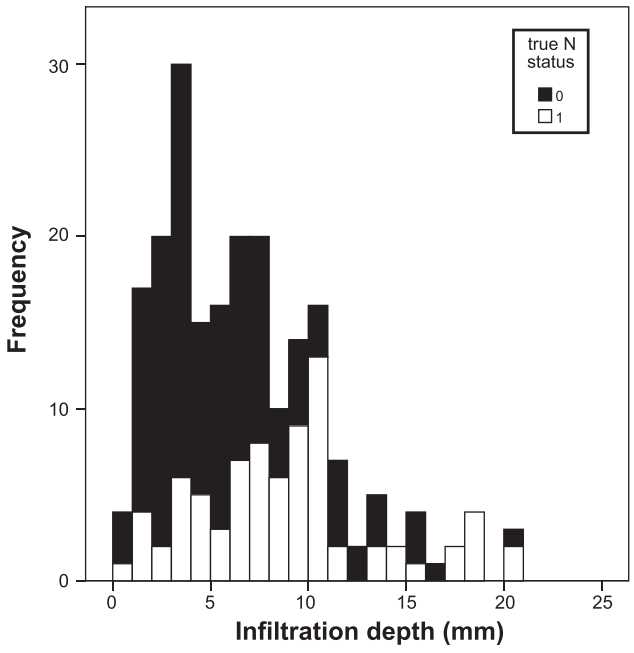

Figure 1 Histogram showing the distribution of infiltration depth ($n = 212$).

watchful waiting group ($n = 38$), infiltration depth was the only significant predictor, the other variables were constant.

Therefore, we concluded that infiltration depth is an independent predictor for the true N status in pT1–2 OSCC.

4.59 mm is the most optimal infiltration depth cut-off for performing a neck dissection

To be of use as a clinical decision tool for performing an elective neck dissection, a cut-off depth should be determined that discriminates optimally between tumours with a large infiltration depth and high risk for nodal metastases, and tumours with a small infiltration depth and low risk for nodal metastases. Because watchful waiting is considered an eligible treatment only in pT1cN0 tumours, a ROC-analysis was performed on this subgroup ($n = 106$). A clear cut-off was found at an infiltration depth of 4.59 mm (OR = 8.3; 95%CI: 2.2–31.0), with a sensitivity of 83.3% and a specificity of 62.5% (Table 3). For the watchful waiting group the cut-off of 4.59 mm (OR = 8.6; 95%CI: 1.4–54.2) resulted in a sensitivity of 71.4% with a specificity of 77.4%, a positive predictive value (PPV) of 41.7% and a negative predictive value (NPV) of 92.3% (Table 3).

Using 4.59 mm as cut-off does not result in higher overtreatment rates

To illustrate the effectiveness of using infiltration depth $\geqslant$4.59 mm as additional indication for treating the neck, we looked at the watchful waiting patients ($n = 38$) in more detail.

If every watchful waiting patient with an infiltration depth of $\geqslant$4.59 mm would be treated with a neck dissection, this would result in additional neck treatments of 12 patients, of which 7 (58%) would be overtreated, and 5 patients (42%) would be correctly treated. In total 29 patients (76%) would be correctly treated with either neck dissection or watchful waiting (Table 3). Comparing these numbers with the neck treated group ($n = 174$), shows that the percentage overtreated cases is comparable (59% in neck treated group) and that the percentage correctly treated cases (76% vs. 41% in the neck treated group) is much higher when using the infiltration depth cut-off of 4.59 mm.

Deeper infiltration is associated with shorter survival

We analyzed disease specific survival data for all tumours ($n = 212$). There was a significant shorter disease specific survival (DSS) in cN+ tumours ($p < 0.001$; Fig. 2A). Regarding primary tumour site, there were no differences in DSS when comparing

Table 2
Univariate regression with true N status.

Variable		All cases (n = 212)		Neck treated population (n = 174)		Watchful waiting (n = 38)	
		Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
cN status	0	1	7.7–41.1	1	7.0–38.9	–	–
	+	17.7		16.5			
pT status	1	1	1.6–5.2	1	1.3–4.5	–	–
	2	2.9		2.4			
Perineural invasion	no	1	2.0–9.8	1	2.1–11.5	–	–
	yes	4.4		4.9			
Lymphovascular invasion	no	1	2.0–17.0	1	1.7–15.3	–	–
	yes	5.8		5.1			
Infiltration depth	Per mm	1.2	1.1–1.3	1.2	1.1–1.2	1.5	1.1–2.2

All assessed with univariate logistic regression. Infiltration depth is continuous (per millimetre). CI: confidence interval. –: Could not be assessed because these variables were constant.

Table 3
Statistics for different cut-off values.

Infiltration depth cut-off (mm)	pT1cN0 (n = 106)				Watchful waiting cases (n = 38)							
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Patients to treat with END (%)	No. of patients correctly treated by END or WW	No. of patients over treated	No. of patients under treated
1	100	3.4	17.5	100	100	3.2	18.9	100	37 (97)	8	30	0
2	94.4	17.0	18.9	93.8	85.7	19.4	19.4	85.7	31 (82)	12	25	1
3	88.9	35.2	21.9	93.9	71.4	51.6	25.0	88.9	20 (53)	21	15	2
4	83.3	56.8	28.3	94.3	71.4	77.4	41.7	92.3	12 (32)	29	7	2
4.59	83.3	62.5	31.3	94.8	71.4	77.4	41.7	92.3	12 (32)	29	7	2
5	72.2	63.6	28.9	91.8	57.1	77.4	36.4	88.9	11 (29)	28	7	3
6	66.7	73.9	34.3	91.5	57.1	83.9	44.4	89.7	9 (24)	30	5	3
7	50.0	81.8	36.0	88.9	57.1	93.5	66.7	90.6	6 (16)	33	2	3

PPV = positive predictive value; NPV = negative predictive value; END = elective neck dissection; WW = watchful waiting.

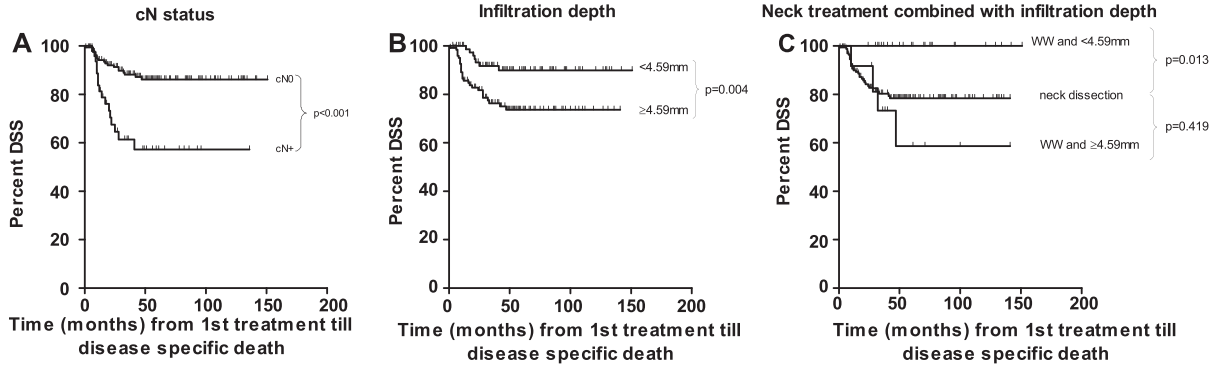

Figure 2 Kaplan–Meier analyses on total group (n = 212). (A) Kaplan–Meier analysis of DSS vs. cN status. HR cN+ = 3.5; 95%CI: 1.8–6.8. HR cN0 = 1. (B) Kaplan–Meier analysis of DSS vs. infiltration depth <4.59 vs. ⩾4.59 mm. HR ⩾ 4.59 mm = 3.2; 95%CI: 1.4–7.2. HR < 4.59 mm = 1. (C) Kaplan–Meier analysis of DSS of WW combined with infiltration depth ⩾4.59 vs. < 4.59 mm vs. neck treated group. HR WW and <4.59 mm = 0.04; 95%CI: 0.001–2.2; HR WW and ⩾4.59 mm = 1.5; 95%CI: 0.5–4.3. HR neck dissection = 1. p-values of log-rank analysis. Survival in months. DSS = disease specific survival; WW = watchful waiting; HR = hazard ratio.

tongue, gum, floor of mouth and other sites. Perineural and lymphovascular invasion were both significantly associated with shorter DSS. A difference in DSS was found between ⩾4.59 and <4.59 mm infiltration depth when analyzing all tumours (p = 0.004; Fig. 2B), and when analyzing only tumours of the watchful waiting group (p = 0.001), but not when analyzing only the neck treated population (p = 0.103). In the watchful waiting tumours all disease specific deaths occurred in the group with ⩾4.59 mm infiltration depth.

Combining these findings in one model shows that within the watchful waiting group an infiltration depth <4.59 mm identifies a specific subgroup, that has a significantly better survival than the watchful waiting group with an infiltration depth ⩾4.59 mm (p = 0.001), and that the watchful waiting group with an infiltration depth ⩾4.59 mm has a DSS that is not significantly different from the neck treated group (p = 0.419; Fig. 2C).

Discussion

This retrospective study shows that infiltration depth is an independent predictor for the presence of nodal metastasis in our well documented series of 212 pT1–2 oral squamous cell carcinomas (OSCC). A clear cut-off for predicting nodal metastases in pT1cN0 OSCC was found at an infiltration depth of 4.59 mm.

In literature, different definitions of infiltration depth are used. In a review paper on infiltration depth and tumour thickness in

OSCC, more than fifty studies, published since 1984 were included.[10] More than half of these studies did not clearly explain whether infiltration depth or tumour thickness was measured. Six studies measured infiltration depth,[12,22–26] as in the present study. Infiltration depth is considered a better predictor for nodal status, because it compensates for exophytic growth or tissue destruction by the tumour.[12,14–16,21] Since the 2005 review, five more studies on infiltration depth were published.[13,14,27–29] The average number of included patients in these 11 studies was 50. Two studies did not find a significant cut-off value for the prediction of nodal metastases,[14,27] despite infiltration depth being significant in multiple regression analysis in one.[14] One study found a significant cut-off at 2.2 mm.[13] This study also had a small overall infiltration depth (mean of 2.3 mm). This might be due to the very small study population ($n = 27$). The other eight studies all found a significant cut-off in the range 4–5.5 mm, in good agreement with our data. Of these eight studies, only two described a rationale for the cut-off that was chosen.[23,28] The other studies did not describe why they chose a certain cut-off.[12,22,24–26,29] None used objective statistical methods to determine the most optimal cut-off based on its predictive characteristics (e.g. a ROC-analysis).

In this study we demonstrated that infiltration depth is an independent predictor for nodal metastases in pT1–2 OSCC. ROC-analysis was performed on the group with the most potential benefit from the implementation of infiltration depth: pT1cN0 OSCC. Performing ROC-analysis on the in literature frequently studied subgroup of tongue and floor of mouth tumours ($n = 87$), led to a minimally changed cut-off at 4.57 mm (data not shown).

Our infiltration depth cut-off at 4.59 mm resulted in a PPV of 41.7% in the watchful waiting group. However, in head–neck oncology literature, an elective neck dissection is generally recommended in cN0 patients when the risk for metastasis is considered greater than 20%.[5] Applying this 20% rule to our data would result in a cut-off at an infiltration depth of approximately 2 mm (PPV = 19.4% in watchful waiting group; Table 3). This is not a practical cut-off for three reasons. First, treating all watchful waiting patients with a tumour infiltration depth $\geqslant$2 mm, would result in a large increase in performed neck dissections, and associated healthcare costs, as this infiltration depth concerns 82% of the watchful waiting patients. Secondly, this would result in a high overtreatment rate of 81% of all treated patients. Thirdly, this treatment would probably not result in an increased survival, as there is no DSS difference between the <2 mm and $\geqslant$ 2 mm infiltration depth groups (data not shown).

The determination of the true N status in our population was strict, only accepting histologically confirmed pN status or cN status after $\geqslant$ 2 years of follow-up. However, there is a chance that metastases were not removed from the neck by the surgeon or were missed by the pathologist when examining the neck dissection specimen.[30] Therefore, we also analyzed the follow-up of pN0 cases.

In the 102 pN0 cases in our series (median follow-up 45 months), there were 7 cases (7%) that developed a regional recurrence during follow-up. Two developed contralateral level I metastases (both border-of-tongue tumours <4.59 mm infiltration). Three cases developed metastases contralaterally in lower levels, and two cases developed metastases on the treated side of the neck (all five cases had an infiltration depth $\geqslant$4.59 mm). Performing a re-analysis with these 7 cases changed to pN+ however, does not change the cut-off of 4.59 mm.

There is still a possibility for false pN0 if micrometastases were completely removed by neck dissection, but subsequently missed by the pathologist. This possibility can never be completely ruled out, not even by step serial sectioning.[31] However, we expect this possible scenario to have minimal effect on the proposed infiltration depth cut-off. Even more because in these cases metastatic cells are completely removed and survival is comparable to N0 cases.[32]

All measurements were performed on formalin-fixed, paraffin embedded (FFPE) tumour resection material. Because of the shrinkage associated with this fixation process,[33] the cut-off is not readily applicable to, for example, fresh frozen tissue.[34] Infiltration depth is determined by the pathologist postoperatively. Therefore, when a neck dissection is indicated (infiltration depth $\geqslant$4.59 mm), this has to be performed in a second procedure.

Sentinel lymph node biopsy (SNB) can be performed using intra-operative cryosectioning, therefore eliminating the need for a second procedure. However, single tumour cells and small fields can easily be missed on frozen sections and immunohistochemistry can not be performed at the time of surgery. As most SNB studies are performed on FFPE material,[35] it is not clear if predictive values will hold on frozen material.[36] The NPV of an infiltration depth cut-off at 4.59 mm (94.8%) is comparable to that found in most recent SNB studies.[37–39] Moreover, infiltration depth can be assessed in every tumour, whereas in SNB failure to identify the sentinel node, is reported in up to 10% of procedures.[37–39]

The economical costs of implementing infiltration depth as an absolute indication for performing a neck dissection are beyond the scope of this paper, but the costs for extra neck dissections may be balanced by savings on frequent follow-up and imaging due to fewer watchful waiting patients. Fewer patients are being undertreated, and consequently there will be less need for costly salvage surgery, with associated poor outcome.

The advantages of using infiltration depth as predictor for the nodal status in OSCC are plenty. It is easy, quick and cheap to perform. Infiltration depth, defined as in the current study, is already a standard item in the histopathology report according to the Royal College of Pathologists (UK)[40] and the Dutch Working Group Head–Neck Tumours,[41] amongst others. Therefore, the established cut-off can be readily implemented in clinical practice.

For every-day guidelines for the management of the cN0 neck, a more practical cut-off, in whole millimetres may be considered. We recommend a cut-off at 4 mm, because specificity and sensitivity are only minimally affected from the optimal values at 4.59 mm (Table 3).

In summary, this study shows that infiltration depth is an independent predictor for the presence of nodal metastasis in pT1–2 OSCC, and that 4.59 mm is the most optimal cut-off in pT1cN0 tumours. Infiltration depth was the only independent predictor in watchful waiting tumours. The cut-off of 4.59 mm identifies a subgroup of patients at increased risk for nodal metastasis (OR = 8.3) and with significantly shorter survival. Applying infiltration depth as indication for elective neck dissection in patients currently treated by watchful waiting would result in the correct treatment of 76%, with an overtreatment percentage (58%) comparable to the current neck treated population.

We recommend an infiltration depth of $\geqslant$4 mm to be used as an absolute indication for performing an elective neck dissection in pT1cN0 OSCC.

Conflict of interest statement

None declared.

References

1. Gourin CG, Conger BT, Porubsky ES, Sheils WC, Bilodeau PA, Coleman TA. The effect of occult nodal metastases on survival and regional control in patients with head and neck squamous cell carcinoma. *Laryngoscope* 2008;**118**(7):1191–4.
2. Pitman KT. Rationale for elective neck dissection. *Am J Otolaryngol* 2000;**21**(0196–0709; 1):31–7.

3. Bradley PJ, Ferlito A, Silver CE, Takes RP, Woolgar JA, Strojan P, et al. Neck treatment and shoulder morbidity: still a challenge. *Head Neck* 2010.
4. Rennemo E, Zatterstrom U, Boysen M. Impact of second primary tumors on survival in head and neck cancer: An analysis of 2,063 cases. *Laryngoscope* 2008;**118**(8):1350–6.
5. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg* 1994;**120**(0886–4470; 7):699–702.
6. Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. *Oral Oncol* 2011.
7. Frech S, Hormann K, Riedel F, Gotte K. Lymphatic vessel density in correlation to lymph node metastasis in head and neck squamous cell carcinoma. *Anticancer Res* 2009;**29**(5):1675–9.
8. Longatto Filho A, Oliveira TG, Pinheiro C, de Carvalho MB, Curioni OA, Mercante AM, et al. How useful is the assessment of lymphatic vascular density in oral carcinoma prognosis? *World J Surg Oncol* 2007;**5**:140.
9. Takes RP, Rinaldo A, Rodrigo JP, Devaney KO, Fagan JJ, Ferlito A. Can biomarkers play a role in the decision about treatment of the clinically negative neck in patients with head and neck cancer? *Head Neck* 2008;**30**(1043–3074; 4):525–38.
10. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head Neck* 2005;**27**(12):1080–91.
11. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. *Cancer* 2009;**115**(7):1489–97.
12. O-charoenrat P, Pillai G, Patel S, Fisher C, Archer D, Eccles S, et al. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. *Oral Oncol* 2003;**39**(4):386–90.
13. Warburton G, Nikitakis NG, Roberson P, Marinos NJ, Wu T, Sauk Jr JJ, et al. Histopathological and lymphangiogenic parameters in relation to lymph node metastasis in early stage oral squamous cell carcinoma. *J Oral Maxillofac Surg* 2007;**65**(3):475–84.
14. Kane SV, Gupta M, Kakade AC, D'Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *Eur J Surg Oncol* 2006;**32**(7):795–803.
15. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. *Arch Surg* 1986;**121**(12):1410–4.
16. Gonzalez-Moles MA, Esteban F, Rodriguez-Archilla A, Ruiz-Avila I, Gonzalez-Moles S. Importance of tumour thickness measurement in prognosis of tongue cancer. *Oral Oncol* 2002;**38**(4):394–7.
17. O'Brien CJ, Lauer CS, Fredricks S, Clifford AR, McNeil EB, Bagia JS, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer–but what thickness? *Head Neck* 2003;**25**(11):937–45.
18. Clark JR, Naranjo N, Franklin JH, de Almeida J, Gullane PJ. Established prognostic variables in N0 oral carcinoma. *Otolaryngol Head Neck Surg* 2006;**135**(5):748–53.
19. Wallwork BD, Anderson SR, Coman WB. Squamous cell carcinoma of the floor of the mouth: Tumour thickness and the rate of cervical metastasis. *ANZ J Surg* 2007;**77**(9):761–4.
20. Fritz A. *ICD-O, international classification of diseases for oncology*. 3rd ed. Geneva: World Health Organization; 2000.
21. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. *Head Neck* 1995;**17**(6):463–72.
22. Asakage T, Yokose T, Mukai K, Tsugane S, Tsubono Y, Asai M, et al. Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. *Cancer* 1998;**82**(8):1443–8.
23. Fukano H, Matsuura H, Hasegawa Y, Nakamura S. Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. *Head Neck* 1997;**19**(3):205–10.
24. Kurokawa H, Yamashita Y, Takeda S, Zhang M, Fukuyama H, Takahashi T. Risk factors for late cervical lymph node metastases in patients with stage I or II carcinoma of the tongue. *Head Neck* 2002;**24**(8):731–6.
25. Sparano A, Weinstein G, Chalian A, Yodul M, Weber R. Multivariate predictors of occult neck metastasis in early oral tongue cancer. *Otolaryngol Head Neck Surg* 2004;**131**(4):472–6.
26. Lim SC, Zhang S, Ishii G, Endoh Y, Kodama K, Miyamoto S, et al. Predictive markers for late cervical metastasis in stage I and II invasive squamous cell carcinoma of the oral tongue. *Clin Cancer Res* 2004;**10**(1 Pt 1):166–72.
27. Goerkem M, Braun J, Stoeckli SJ. Evaluation of clinical and histomorphological parameters as potential predictors of occult metastases in sentinel lymph nodes of early squamous cell carcinoma of the oral cavity. *Ann Surg Oncol* 2010;**17**(2):527–35.
28. Keski-Santti H, Atula T, Tornwall J, Koivunen P, Makitie A. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol* 2006;**42**(1368–8375; 1):96–101.
29. Suzuki M, Suzuki T, Asai M, Ichimura K, Nibu K, Sugasawa M, et al. Clinicopathological factors related to cervical lymph node metastasis in a patient with carcinoma of the oral floor. *Acta Otolaryngol Suppl* 2007;**559**(559):129–35.
30. Barrera JE, Miller ME, Said S, Jafek BW, Campana JP, Shroyer KR. Detection of occult cervical micrometastases in patients with head and neck squamous cell cancer. *Laryngoscope* 2003;**113**(5):892–6.
31. Rhee D, Wenig BM, Smith RV. The significance of immunohistochemically demonstrated nodal micrometastases in patients with squamous cell carcinoma of the head and neck. *Laryngoscope* 2002;**112**(11):1970–4.
32. Woolgar JA. Micrometastasis in oral/oropharyngeal squamous cell carcinoma: incidence, histopathological features and clinical implications. *Br J Oral Maxillofac Surg* 1999;**37**(3):181–6.
33. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. *Head Neck* 1997;**19**(4):281–6.
34. Gardner ES, Sumner WT, Cook JL. Predictable tissue shrinkage during frozen section histopathologic processing for mohs micrographic surgery. *Dermatol Surg* 2001;**27**(9):813–8.
35. Sloan P. Head and neck sentinel lymph node biopsy: current state of the art. *Head Neck Pathol* 2009;**3**(3):231–7.
36. Pitman KT, Ferlito A, Devaney KO, Shaha AR, Rinaldo A. Sentinel lymph node biopsy in head and neck cancer. *Oral Oncol* 2003;**39**(4):343–9.
37. Alkureishi LW, Ross GL, Shoaib T, Soutar DS, Robertson AG, Thompson R, et al. Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a european multicenter trial. *Ann Surg Oncol* 2010;**17**(9):2459–64.
38. Broglie MA, Haile SR, Stoeckli SJ. Long-term experience in sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. *Ann Surg Oncol* 2011;**18**(10):2732–8.
39. Keski-Santti H, Kontio R, Tornwall J, Leivo I, Matzke S, Suominen S, et al. Sentinel lymph node biopsy or elective neck dissection for patients with oral squamous cell carcinoma? *Eur Arch Otorhinolaryngol* 2008;**265**(Suppl 1):S13–7.
40. The Royal College of Pathologists. Datasets for histopathology reports on head and neck carcinomas and salivary neoplasms. June 2005 [cited October 27 2011]. Available from: http://www.rcpath.org/resources/pdf/HeadNeckDatasetJun05.pdf.
41. Dutch Working Group Head–Neck Tumours. Guideline oral and oropharyngeal carcinoma. 2004 [cited October 27 2011]. Available from: http://www.cbo.nl/Downloads/287/rlmondholte2004.pdf.